REMARKS

Reconsideration and continuing examination of the above-identified application is respectfully requested in view of the amendments above and the discussion that follows.

Claims 116, 117 and 118, have been amended. Claims 101 through 109 and 116 through 118 are in the case and are before the Examiner.

I. The Amendments

Each of claims 116, 117 and 118 has been amended to recite sequences against which one can compare a sequence for ascertaining the percentage of substitution. Support for this amendment can be found at least at page 47 of the specification.

Each of claims 116-118 has also been amended to recite the conditions under which the chimer particles' protein enhanced stability is measured. This stability is directed at the proteins themselves as is seen from the SDS-PAGE gel results shown in Figs. 3, 4 and 8. Specific support for those recitations can be seen from those figures and least from Paragraphs [0093], [0335-0342], Examples 6, 7, 22 and 23, Paragraphs [0423-0428, and 0429-0436] of the published specification (20040156864).

It is thus seen that no new matter has been added.

II. The Action

A. Withdrawal of Rejections Under 35 USC §112, First and Second Paragraphs

Withdrawal of the previous rejections under 35 USC §112 are noted with appreciation. The new bases for rejection are dealt with below.

B. Rejections Under 35 USC §112, First Paragraph

1. First Rejection

The phrase complained of in paragraphs 18-20 has been deleted to speed prosecution. However, it is noted that the phrase is well supported in the specification as was previously stated in the prior reply. That deleted phrase has been replaced by a further recitation that is also well supported as is discussed above.

It is well settled that claim language need not be present *ipsis verbis or in heac verba* in the specification for that claim language to be supported. See, *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). The purpose of the "WRITTEN DESCRIPTION" section of 35 USC §112 was said in *Vas-Cath* to convey "with reasonable clarity to those skilled in the art that, as of the filing date sought, [the inventor] was in possession of the invention." See, also MPEP section 2163.02 third paragraph, first sentence.

2. Second Rejection

In paragraph 21, the Action has here rejected the phrase "containing no more than about 5 percent conservatively substituted amino acid residues in the HBc sequence" as alleged

new matter. This basis for rejection cannot be agreed with and is respectfully traversed.

It is first noted that "new matter" is a statutorily improper basis for rejection under 35 USC §112. That basis for rejection is better phrased to be for a failure of the description requirement. When properly phrased, it is no better a rejection.

The presently pending dependent claims were originally dependent from independent claims 1, 18, 42 and 79 that were cancelled here because of the restriction. Claim 1 contained the recitation "containing no more than 20 percent conservatively substituted amino acid residues in the HBc sequence", whereas claim 18 contained the recitation "having an amino acid residue sequence in which no more than about 10 percent of the amino acid residues are substituted in the HBc sequence of the chimer", claim 42 recited "having an amino acid residue sequence in which no more than about 5 percent of the amino acid residues are substituted in the HBc sequence of the chimer," and claim 79 recited "said chimer molecules containing no more than 20 percent conservatively substituted amino acid residues in the HBc sequence". It is therefore seen that the originally filed claims contained recitations of 5, 10 and 20 percent substitutions and some were recited as being conservative. Support for the fact that the substitutions are or can be conservative is also noted in paragraphs [0152-0157] of the published application (20030138769) that discuss various aspects of substitutions and begin in paragraph [0152] by asserting that "a contemplated chimer molecule can also contain conservative substitutions in the amino acid residues that constitute HBc Domains I, II, III and IV".

It is thus submitted that the present rejection is without merit as the specification and claims as filed more than amply support the recited claims language. This basis for rejection should therefore be withdrawn.

The Action has also cited *In re Rasmussen*. That citation is inapt for several reasons. First, the citation is incorrect. It should be 211 USPQ 325, not 210 USPQ 325.

Second, and more importantly, Rasmussen discussed a broadening amendment. The amendments complained of here are narrowing amendments.

Third, and more important still, the Court found in favor of the applicant and held that even though he did not have *ipsis verbis* support, the specification's disclosure supported the proposed amendments. The same support should be found here.

C. Rejections Under 35 USC §102(b)

Zlotnick et al.

Withdrawal of the rejection of claims 102, 106, 107 and 117 pursuant to 35 USC §102(b) as anticipated by Zlotnick is noted with appreciation.

D. Rejection Under 35 USC §103(a)

Pumpens in view of Zlotnick

Claims 100-109 and 115-118 were again rejected as allegedly obvious over the disclosures of Pumpens in view of Zlotnick, as in the prior Action. This rejection is respectfully traversed as discussed below.

Following the logic of this Action, only the invention of new elements as was done when Elements 95 and 96 were claimed by the late Glenn T. Seaborg in US Patents No. 3,156,523 and No. 3,161,462, respectively, would be sufficiently free of pre-existing elements to gain patentability. It is submitted that even after the *KSR* decision, a holding of obviousness requires more.

Here, (i) HBc proteins that contained added non-HBc sequences but were unstable on storage existed in the art. It was also known from Zlotnick that (ii) elimination of all internal cysteine residues from a truncated HBc protein plus the addition of a single heterologous residue at the C-terminus produced particles that could better withstand being in a 3.5 M urea denaturing solution than could particles produced from a similar disulfide-reduced protein or a cysteine-free protein. The reported result from that dunking of particles in denaturant for an unspecified time was that the particles containing the C-terminal cysteine stayed together, whereas those without any cysteines were denatured, dissociated and formed two peaks in the size exclusion study shown in Zlotnick's Fig. 2b. The results shown in Fig. 2a indicate that the protein of the cysteine-containing chimers polymerized at pH 9.5 were less pure than that polymerized at pH 7.5.

It is respectfully submitted that Zlotnick is, at worst, silent on the issue of protein stability of chimers with and without cysteines. Indeed, it is rather urged from the extra band seen in the monomer region of lane 7 of Zlotnick's Fig. 2a that having the added cysteine caused a protein stability problem with those chimers. Thus, there were two or possibly three protein bands in lane 7 for the cysteine-

containing chimer, with only one band being seen for any of the cysteine-free proteins.

It is thus submitted that Zlotnick has no teaching related particle stability in the form of protein degradation, as compared to particle dissociation stability. The claims have been amended to clarify that the stability recited relates to the proteins of the particles. That is what the underlying stability data show. Copies of Figs. 3, 4, and 8 are attached to this paper for the Examiner's convenience.

The enhanced stability claimed here does not relate to the equilibrium of monomeric and polymeric forms in the particles themselves as is disclosed by Zlotnick. As such, it is of little moment to the present invention whether "disulfide bond formation by Cp*150 can promote capsid assembly" because capsid assembly does not equate to nor suggest protein stability from degradation on dissolution of chimer protein particles in aqueous buffer at 37^{O} C for about two weeks.

It is reiterated that the before-cited and discussed paper by Ulrich, a worker of at least ordinary skill if not extraordinary skill, that stated that the stability problem of HBc was not solved prior to the application's filing date is particularly relevant here. That is the case is illustrated by the fact that Ulrich had published at least 24 papers since 2002 in viral-related technologies. He was a lead author in this field for years before and after the relied-on publications by Pumpens and Zlotnick. He has published papers co-authored with Pumpens as will be seen in the attached Exhibits that are discussed hereinafter. "It is jurisprudentially inappropriate to disregard any relevant evidence on any issue in any case,

patent cases included." *Stratoflex Inc. v. Aeroquip Corp.*, 218 USPQ 871, 879 (Fed. Cir. 1983).

The Examiner's attention is again invited to *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579; 27 USPQ2d 1200 (1993). The Court noted that the "fact of publication (or lack thereof) in a peer reviewed journal thus will be a relevant, though not dispositive, consideration in assessing the scientific validity of a particular technique or methodology on which an opinion is based." (27 USPQ2d at 1206.)

It is again submitted that Ulrich's writings should be afforded more weight than the unsupported suppositions as to what may be in the mind of a hypothetical person of ordinary skill. Rather, Ulrich is (was) an author of probably greater than ordinary skill. Ulrich wrote in a peer-reviewed paper published after both relied-on documents and before the filing of the instant application's earliest parent application that a problem of chimer usage in vaccines related to the requirement of reproducible preparation of intact chimer particles that were stable and could withstand long-term storage.

Ulrich did not put together the combination of the two teachings to solve the stability problem that he wrote about, but rather maintained that the problem still had to be solved. Ulrich, Pumpens and other authors published enclosed Exhibit I [Lachmann et al., *Intervirology* 1999; **42**:51-56] about a year prior to the filing of the earliest parental application here and cited the relied-on Zlotnick paper as note [16]. Counsel has found a single reference to [16] and that is on page 55. The point for which Zlotnick was cited is the following:

> Similarly, C-terminal fusions [of inserted peptide sequences] were found again to be lower immunogenic [sic] than c/e1 insertions [8]. These data are in line with structural data suggesting a luminal localization of the C-terminal region [16].

It is submitted that if Ulrich the real, live worker of more than ordinary skill working and writing in this art did not put together the relied-on art as has the hypothetical skilled worker of the Action, the Action is mistaken in its conclusion as to the abilities of its hypothetical worker and obviousness, and that conclusion of obviousness should be withdrawn.

In another published paper entitled "Stability and Morphology Comparisons of Self-Assembled Virus-Like Particles from Wild-Type and Mutant Human Hepatitis B Virus Capsid Proteins" Newman et al., *J. Virol.*, Dec. 2003; **77(24):**12950-12960, (enclosed Exhibit II), the authors cited the Zlotnick paper at page 12959 as note (39) for

> [u]sing spectrophotometric measurement, Zlotnick et al. estimated the stoichiometry of encapsidated RNA and *E. coli*-derived capsid particles to be near a total of 3,000 ribonucleotides per full-length capsid particle (95% T=4) (39).

The Abstract of that paper states in part:

> [w]e found no significant differences in capsid stability between wild-type and mutant I97L particles [those whose isoleucine at position 97 was mutated to a leucine] under denaturing pH and temperature in either full-length or truncated core protein contexts. In general, HBV capsid particles (HBcAg1-183, HBcAg1-149, and HBcAg1-140) are very robust but will

> dissociate at pH 2 or 14, at temperatures higher than 75°C, or in 0.1% sodium docecyl sulfate (SDS).

The lead (corresponding) author of Newman et al. is Dr. Chiao Shih, a full Professor in the Departments of Pathology and of Microbiology and Immunology at the University of Texas Medical Branch. Examination of his profile, which was obtained from the University web site and is attached as Exhibit III, shows that he as been the lead author of several peer-reviewed articles dealing with hepatitis B core. It must be agreed that the Newman et al. paper is concerned with particle stability from its title and the second quote above. Thus, from the above quotes, we have another worker of more than ordinary skill in the art who cited the Zlotnick paper, but failed to make the connection that is asserted to be obvious to a worker of lesser skill; i.e., ordinary skill. It is again submitted that this basis for rejection should be withdrawn.

E. Additional Information That May Be Material

In view of the holding in *McKesson Information Solutions, Inv. V. Bridge Medical, Inc.* (Fed. Cir. May 18, 2007; 06-1517), enclosed herewith are copies of Actions from an application relating to recombinant hepatitis B core particles and their use that might be deemed material to the prosecution of the present application. It is noted that the Examiner handling this application is also handling divisional applications Serial No. 10/805,913 and Serial NO. 10/806,006, as well as applications Serial No. 10/732,862 and Serial No. 10/787,734, so the Actions from those applications are not being included herewith. The enclosed Actions are from Application

Serial No. 10/677,074, and are noted on enclosed Form PTO/SB/08B.

F. Summary

Claims 116, 117 and 118 have been amended. Each of the bases for rejection has been dealt with and overcome or otherwise made moot.

It is therefore believed that this application is in condition for allowance of all of the pending claims. An early notice to that effect is earnestly solicited.

A fee for the filing of the Actions from the other application is enclosed. No further fee or petition is believed to be necessary. However, should any further fee be needed, please charge our Deposit Account No. 23-0920, and deem this paper to be the required petition.

The Examiner is requested to phone the undersigned should any questions arise that can be dealt with over the phone to expedite this prosecution.

Respectfully submitted,

By 

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Enclosures
- Exhibits I-III.
- Petition and Fee
- IDS Fee for filing Actions
- Actions from other application, Form PTO/SB/08B
- Figs. 3, 4, and 8